



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 15g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis
(Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lactic Acidosis	<p>NRTIs:</p> <ul style="list-style-type: none"> • ZDV • Less likely with 3TC, FTC, ABC, TAF, and TDF <p>Other Drugs:</p> <ul style="list-style-type: none"> • See the Risk Factors and Prevention/Monitoring columns for information regarding the toxicity of propylene glycol when LPV/r oral solution is used in neonates. 	<p>Onset:</p> <ul style="list-style-type: none"> • Generally after years of exposure <p>Presentation:</p> <ul style="list-style-type: none"> • Lactic acidosis may be clinically asymptomatic. <p><i>Lactic Acidosis May Also Present with Insidious Onset of a Combination of Signs and Symptoms:</i></p> <ul style="list-style-type: none"> • Generalized fatigue, weakness, and myalgias • Vague abdominal pain, weight loss, unexplained nausea, or vomiting • Dyspnea • Peripheral neuropathy <p>Note: Patients may present with acute multi-organ failure (e.g., fulminant hepatic failure, pancreatic failure, respiratory failure).</p>	<p>Lactic acidosis is associated with use of ddI and d4T. Cases are rare now that these NRTIs are no longer recommended.</p> <p>3TC, FTC, ABC, TAF, and TDF are less likely to induce clinically significant mitochondrial dysfunction than ZDV.</p>	<p>Adults:</p> <ul style="list-style-type: none"> • Female sex • High BMI • Chronic HCV infection • African-American race • Coadministration of TDF with metformin • Overdose of propylene glycol • CD4 count <350 cells/mm³ • Acquired riboflavin or thiamine deficiency • Possibly pregnancy <p>Preterm Infants or Any Neonates Who Have Not Attained a Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days:</p> <ul style="list-style-type: none"> • Exposure to propylene glycol, which is used as a diluent in LPV/r oral solution. A diminished ability to metabolize propylene glycol may lead to accumulation, increasing the risk of adverse events. 	<p>Prevention:</p> <ul style="list-style-type: none"> • Due to the presence of propylene glycol as a diluent, LPV/r oral solution should not be used in preterm neonates or any neonate who has not attained a postmenstrual age of 42 weeks and a postnatal age of ≥14 days. • Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. <p>Monitoring</p> <p><i>Asymptomatic Patients:</i></p> <ul style="list-style-type: none"> • Measurement of serum lactate is not recommended. <p><i>Patients with Clinical Signs or Symptoms Consistent with Lactic Acidosis:</i></p> <ul style="list-style-type: none"> • Obtain blood lactate level.^a • Additional diagnostic evaluations should include serum bicarbonate, anion gap, and/or arterial blood gas; amylase and lipase; serum albumin; and hepatic transaminases. 	<p>For Patients with Lactate 2.1–5.0 mmol/L (Confirmed with a Second Test):</p> <ul style="list-style-type: none"> • Consider discontinuing all ARV drugs temporarily while conducting additional diagnostic workup. <p>For Patients with Lactate >5.0 mmol/L (Confirmed With a Second Test)^b or >10.0 mmol/L (Any One Test):</p> <ul style="list-style-type: none"> • Discontinue all ARV drugs. • Provide supportive therapy (e.g., IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). <p>Anecdotal (Unproven) Supportive Therapies:</p> <ul style="list-style-type: none"> • Administer bicarbonate infusions, THAM, high doses of thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) <p>Following the resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen. Institute a revised NRTI-containing regimen with caution, using NRTIs that are less likely to induce mitochondrial dysfunction (ABC, TAF, TDF, FTC or 3TC). Lactate should be monitored monthly for ≥3 months.</p>

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^a Blood for lactate determination should be collected, without prolonged tourniquet application or fist clenching, into a pre-chilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

^b Management can be initiated before receiving the results of the confirmatory test.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane; ZDV = zidovudine

References

General Reviews

- Fortuny C, Deya-Martinez A, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S36-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25629891>.
- Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. *J Med Toxicol*. 2014;10(1):26-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23963694>.
- Tukei VJ, Asiimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *J Acquir Immune Defic Syndr*. 2012;59(3):274-280. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22126740>.
- Bartlett AW, Mohamed TJ, Sudjaritruk T, et al. Disease- and treatment-related morbidity in adolescents with perinatal HIV infection in Asia. *Pediatr Infect Dis J*. 2019;38(3):287-292. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30281549>.
- Tshamala HK, Aketi L, Tshibassu PM, et al. The lipodystrophy syndrome in HIV-infected children under antiretroviral therapy: a first report from the Central Africa. *Int J Pediatr*. 2019;2019:7013758. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30941184>.
- Smith ZR, Horng M, Rech MA. Medication-induced hyperlactatemia and lactic acidosis: a systematic review of the literature. *Pharmacotherapy*. 2019;39(9):946-963. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31361914>.

Risk Factors

- Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivannis P. Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV infection. *J Ren Care*. 2011;37(1):25-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21288314>.
- Lopinavir/ritonavir (Kaletra) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021251s055,021906s050lbl.pdf.
- Firnhaber C, Smeaton LM, Grinsztejn B, et al. Differences in antiretroviral safety and efficacy by sex in a multinational randomized clinical trial. *HIV Clin Trials*. 2015;16(3):89-99. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25979186>.
- Fortuin-de Smidt M, de Waal R, Cohen K, et al. First-line antiretroviral drug discontinuations in children. *PLoS One*. 2017;12(2):e0169762. Available at: <https://>

www.ncbi.nlm.nih.gov/pubmed/28192529.

12. Lim TY, Poole RL, Pageler NM. Propylene glycol toxicity in children. *J Pediatr Pharmacol Ther.* 2014;19(4):277-282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25762872>.
13. Mamiafo CT, Moor VJ, Nansseu JR, Pieme CA, Tayou C, Yonkeu JN. Hyperlactatemia in a group of HIV patients living in Yaounde-Cameroon. *AIDS Res Ther.* 2014;11(1):2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24428886>.
14. Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. *PLoS One.* 2011;6(4):e18736. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21494566>.
15. Moren C, Noguera-Julian A, Garrabou G, et al. Mitochondrial evolution in HIV-infected children receiving first- or second-generation nucleoside analogues. *J Acquir Immune Defic Syndr.* 2012;60(2):111-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22362155>.
16. Tetteh RA, Nartey ET, Lartey M, et al. Association between the occurrence of adverse drug events and modification of first-line highly active antiretroviral therapy in Ghanaian HIV patients. *Drug Safety.* 2016;39(11):1139-1149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27638659>.
17. Wester CW, Eden SK, Shepherd BE, et al. Risk factors for symptomatic hyperlactatemia and lactic acidosis among combination antiretroviral therapy-treated adults in Botswana: results from a clinical trial. *AIDS Res Hum Retroviruses.* 2012;28(8):759-765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22540188>.

Monitoring and Management

18. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS Soc.* 2013;16:18600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23782481>.
19. Claessens YE, Cariou A, Monchi M, et al. Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with L-carnitine. *Crit Care Med.* 2003;31(4):1042-1047. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12682470>.
20. Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med.* 2014;371(24):2309-2319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25494270>.
21. Marfo K, Garala M, Kvetan V, Gasperino J. Use of Tris-hydroxymethyl aminomethane in severe lactic acidosis due to highly active antiretroviral therapy: a case report. *J Clin Pharm Ther.* 2009;34(1):119-123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19125910>.
22. Jung B, Martinez M, Claessens YE, et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care.* 2019;9(1):92. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31418093>.